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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,568	02/17/2006	Michael Betz	BP/G-32575A/BCK	5276

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SANDOZ INC
506 CARNEFIE CENTER
PRINCETON, NJ 08540

EXAMINER	
STOICA, ELLY GERALD	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
03/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,568	BETZ ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,12,13,15,18 and 21-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,12,13,15,18 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/07/2005 and 06/01/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement filed 06/01/2007 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The references AS, AT, and BS have been crossed out for not being cited properly and could not be evaluated.

Status of the claims

2. Claims 1-3, 5-8, 12, 13, 15, 18 and 21-29 are pending.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and the independent claim and claims 2-3, 5-8, 12, 13, 15, 18 and 21-29 as dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 1 recites a desired tonicity, but includes no ingredient to attain such; since “consisting essentially of” should include all relevant ingredients, the claim is incomplete.

Claim 21 and 22 recites the limitation "the optional tonicity-adjusting agent" in line 2 of both claims. Since the claims are both dependent on claim 1 and there is no

indication of an ingredient for attaining isotonicity in claim 1 there is insufficient antecedent basis for this limitation in the claims.

Claims interpretation

Regarding the limitations of the independent claim 1 it should be noted that such a limitation as "multi dosage" only implies that the compoisition is not in a syringe yet, as whether or not something is multi-dosage depends on the dosage one intends to administer, which is not specified.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-3, 5-8, 12, 13, 15, 18 and 21- 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor et al. (U.S. Pat. No. 5,763,394) in view of Asgharian B. (WO/99/06023, 11-1999).

The claims are drawn to a multi-dosage liquid pharmaceutical formulation of human growth hormone (hGH) consisting essentially of:

a) about 5 mg/ml to about 100 mg/ml hGH,

b) 1, 2-propylene glycol 0.5mg/ml to about 20 mg/ml

c) an aqueous buffer,

d) a non-ionic surfactant, and

e) a preservative,

wherein the formulation has a tonicity of from about 100 mOsm/kg to about 500 mOsm/kg, pH of from about 6.1 to about 6.3. Preferably, the aqueous buffer is a phosphate, citrate, acetate, or formate buffer and the non-ionic surfactant is poloxamer 188 or a polysorbate at about 0.05 to about 4 mg/ml. Most preferably, the aqueous buffer is a phosphate buffer and the non-ionic surfactant is poloxamer 188. The tonicity-adjusting agent is selected from the group consisting of sugar, a sugar alcohol, a polyol a neutral salt, and an amino acid, preferably mannitol. The preservative is selected from a group consisting of benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, phenol, benzalkonium chloride, benzethonium chloride, chlorobutanol, 2-phenoxyethanol, phenyl mercuric nitrate and thimerosal. The formulation is substantially isotonic and has a pH of about 6.2.

O'Connor et al. teach a stable pharmaceutically acceptable aqueous formulation containing human growth hormone, a buffer, a non-ionic surfactant, and, optionally, a neutral salt, mannitol, or a preservative. Also disclosed are associated means and methods for preparing, storing, and using such formulations (abstract).

Essentially disclosed is a human growth hormone formulation consisting of (claim 9):

a) 1mg/ml to 20 mg/ml hGH,

b) a preservative,

c) a buffer system to provide a pH of 5.5 to 7,

d) 0.1% w/v to 1% w/v non-ionic surfactant, and

e) 50 mM to 200 mM neutral salt

O'Connor et al. further disclose the buffer is selected from the group consisting of citrate, phosphate and acetate buffers (claim 16)) which are all aqueous buffers, and is most advantageously in the range of about 2 mM to about 50 mM (column 3, lines 46-48). O'Connor et al. further disclose the non-ionic surfactant is poloxamer 188, poloxamer 184, or polysorbate (claims 11 and 12) in a concentration range of 0.1% to 5% (w/v), which is 1-50 mg/ml. (col. 3, lines 35-39). O'Connor et al. further disclose preservatives like phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalconium chloride, and benzethonium chloride (column 3, lines 50-54). O'Connor et al. further disclose that about 5 mg/ml to about 50 mg/ml mannitol may be included in the aqueous hGH formulations, as opposed to the neutral salts (column 3, lines 62-64). O'Connor et al. further disclose a directly injectable hGH formulation consisting essentially of: a) 5mg/ml hGH, b) 0.5 mg/ml phenol, c) 2.5 mg/ml sodium citrate

(aqueous buffer), d) 2.0 mg/ml polysorbate 20 (non-ionic surfactant), and e) 8.8 mg/ml sodium chloride (neutral salt/tonicity agent) wherein the hGH formulation is at a pH of 6 (claim 18) and the buffer concentration range is chosen to minimize deamidation, aggregation and precipitation of hGH (col. 3, lines 59-61). O'Connor et al. further disclose that the formulation is adjusted to near isotonicity with saline solutions, depending on the other ingredients present in the formulation (column 4, lines 1-5). The osmolarity is an inherent property to the tonicity adjusting reagents. As disclosed by O'Connor, the concentration range of the hGH in the formulation is not critical and may be varied by the clinician administering the drug (col. 3, line 19-25). O'Connor et al are silent about specifically using 1, 2-propylene glycol in their formulations even though they mention using polyols in their formulations.

Asgharian teaches topical ophthalmic compositions which provide controlled administration of a drug to the eye (p.3, lines 14-16). Further, the pharmaceutical compositions include tonicity agents such as salts (sodium chloride, potassium chloride and calcium chloride) or non- ionic tonicity agents such as propylene glycol (p. 10, lines 3-7). In Example 4, the amount of propylene glycol used is 14 mg/ml.

As presented supra, O'Connor et al. teach all the basic limitations of claims, less the specific use of propylene glycol either for tonicity purposes or other purposes. Asgharian specifically teaches the use of propylene glycol for tonicity adjustment or other purposes (offering even a concentration that is in the range claimed in the instant Application). The optimization of pH and tonicity values are routine in the art for pharmaceutical formulation as suggested also by O'Connor. Therefore, it would

have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the teachings of O'Connor et al., combined with the teachings of Asgharian to obtain the formulations of the instant Application, with a reasonable expectation of success. That is because O'Connor teaches the elements and the ranges of the hGH formulations and Asgharian singles out the use of 1, 2 propylene glycol for tonicity adjustment. By following these teachings the skilled artisan would have applied the existent knowledge in the art. A person of ordinary skill in the art is always motivated to pursue known options within the art and, if this leads to anticipated success, it is likely the product not of innovation but of the ordinary skill and common sense. This is especially true since the Applicant does not present any evidence of the criticality of the ranges of values claimed which were common in the art.

Conclusion

7. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/, Ph.D.

Primary Examiner, Art Unit 1647